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PATHOGENESIS OF NEOPLASIA

Reading: Basic Pathology, Chapter 6 pp 178-201.

Summary: The genesis of neoplasms (oncogenesis) involves multiple genetic and environmental factors, including tumor suppressor genes, genes normally associated with cell growth (oncogenes), or carcinogens. Sometimes oncogenesis is associated with quantitative or qualitative changes in oncogene expression.

I. HISTORY OF THE "MILK FACTOR".
   A. In C_3H mice females develop breast tumors at an early age, but castrated females do not.
      1. Therefore, there are hormonal (environmental) and hereditary factors involved as only some mouse strains develop tumors.
   B. However, foster feeding studies indicated that some factor in milk was responsible. This turned out to be mouse mammary tumor virus (MMTV).
      1. Therefore, there is also a viral etiology to these tumors.
   C. More recently, it has been shown that a segment of MMTV alters the expression of a gene of host origin (an oncogene) that is involved in tumor induction, with amplification by steroids.
   D. Therefore, many factors are involved in tumor formation.

II. CARCINOGENESIS. Cancer is a genetic & environmental disease.
   A. Inherited and childhood tumors: involve gene deletions; more than 20 hereditary cancer syndromes defined and attributed to specific germline mutations. These often act like recessive characteristics in classical genetics - concept of tumor suppressor genes. About 15 such genes described.
      1. Two hit theory - all body cells are heterozygous for allele. Tumor cells do not express gene at all. Suggests loss of tumor suppressor locus.
      2. Examples: retinoblastoma, 13q14; multiple colon polyps, 5q21.
      3. Other examples of tumor suppressor genes
         a. Rb gene - a cell cycle control factor that sits on the site regulating cyclin activity. Phosphorylation of p53 releases transcription factor E2F.
         b. p53 - gene activated by damage to DNA. Induces DNA repair and p21 inhibitor of mitosis or bax, a potentiator of apoptosis. P53 expression has a bad aspect – it accelerates aging.
      4. Other inherited predispositions to cancer - familial cancers & defective DNA repair syndromes. Colon cancer and adenomatous polyposis (APC) gene.
      5. Viral carcinogenesis by DNA viruses often involves inhibition of p53 and Rb activity. Example: carcinoma of the cervix.

   B. Environmental factors. Complex interaction of heredity and environment. Chemical carcinogens-an enormous variety of chemicals may induce tumors. Pott's observations on London chimney sweeps.Geographic pathology – high incidence in Japan of gastric cancer due to <u>H. pylori</u> infection and of liver cancer due to Hepatitis B infections
      1. Major classes of chemical carcinogens.
      2. Characteristics of these substances.
         a. some act directly; some require activation, often by P-450 liver enzymes - highly inducible enzyme systems in some smokers result in increased lung cancer incidence.
         b. dose dependence
         c. mutagens - DNA target - Chromosomal changes. <u>Ames test</u> for carcinogens by mutagenesis of <u>Salmonella</u> sp. Other tests include mutagenesis in mouse lymphoma cells or induction of chromosomal

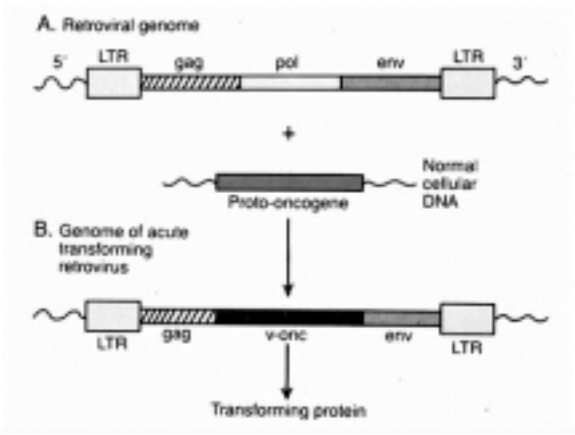
aberrations.

d. cell proliferation enhances carcinogenesis

3. Initiation & promotion of tumors
    a. initiation - a single exposure to an initiator gives rise to rapid changes. Initiators are mutagens and carcinogenic alone. example: methylcholanthrene.
    b. promotion - if given after initiation & for prolonged periods, result in potentiation of initiator effect. They stimulate cell replication, but are not carcinogens when given without initiator. ex. croton oil (phorbol ester, PMA).
    c. precancerous disorders such as persistent regenerative cell replication, dysplastic proliferation, atrophic gastritis, ulcerative colitis, colonic adenomas, and leukoplakia. Clonal origin of many cancers. Concept of tumor progression - bad gets worse.

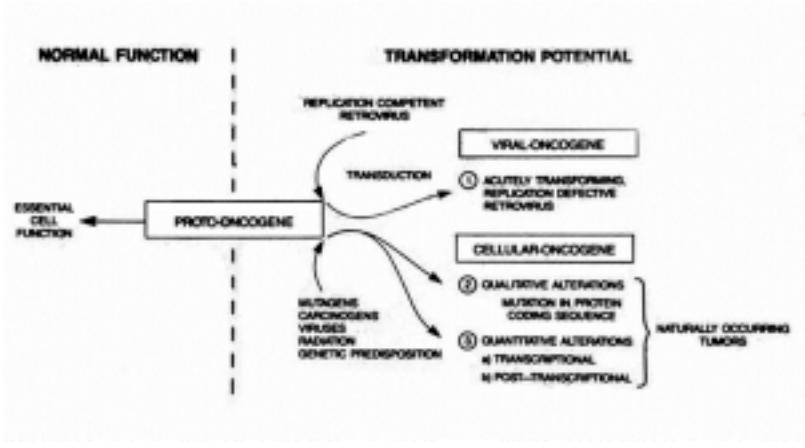
C. Radiation carcinogenesis
1. UV light and skin tumors
    a. mutagenic effect of UV due to pyrimidine dimmer formation. Actinic (solar) keratosis is a precancerous lesion.

D. Viral carcinogenesis
1. Tumors are induced by many types of DNA viruses - papovaviruses, herpesviruses, adenoviruses, poxviruses. Mechanism often involves binding of tumor suppressor gene product by viral protein.
2. Retroviruses - a family of RNA viruses that possess a reverse transcriptase (RNA-dependent DNA polymerase) in the virus structure; during virus growth, viral produced DNA becomes integrated into the host cell DNA, insertional mutagenesis. Members of this group often are associated with lymphomas, leukemias, and other tumors in animals. In humans T-cell leukemia viruses (HTLVs) and HIV are pathogens (Figure 1). HTLV induces leukemia by augmenting IL-2 and GM-CSF production.



III. ONCOGENES: Many retroviruses carry oncogenes (oncs) which act like dominant genes, and are responsible for neoplastic transformation.

A. Various Oncogenes (Figure 2)
1. Viral oncogenes. DNA sequences in the viral gene responsible for tumor formation. These were not originally viral; they are animal genes. Are tumorigenic due to transduction. No cancers in humans are known to be due to viral oncogenes.

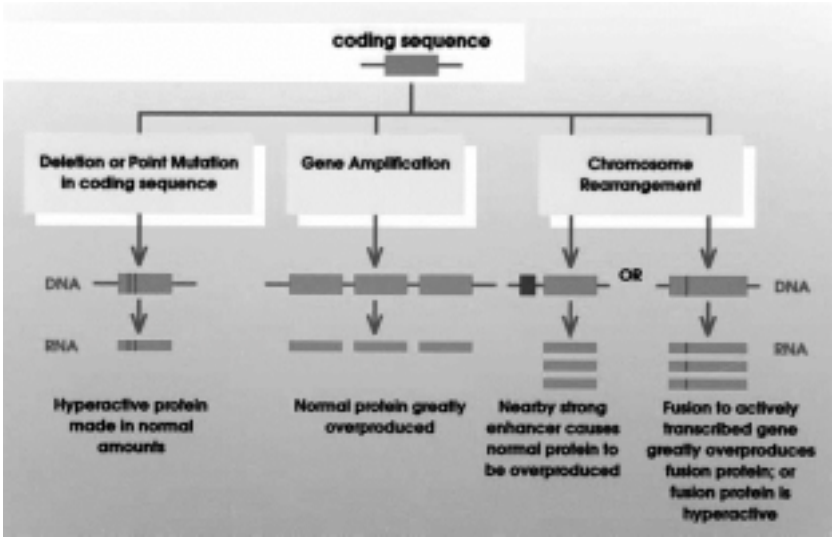


2. Cellular or proto-oncogenes - DNA sequences in normal cells homologous to viral oncogenes. Can be activated by several processes. Most proto-oncogenes never appear in viruses.
    a. Tumor oncogenes - DNA sequences in tumor cells responsible for tumor

formation. They can transform cells experimentally by transfection (transfer of genetic information from one cell to another by uptake of extracted DNA).

B. Discovery of Oncogenes.
   1. Hereditary nature of cancer.
   2. Viruses as inducers of tumors.
      a. In the case of virus-induced transformation, only a fragment of the viral genome (the viral oncogene) is involved in oncogenesis.
      b. The normal cellular homologues of these viral oncogenes are highly conserved. The gene products of several viral oncogenes are enzymes that catalyze transformation events. In some cases the onc product is found at elevated levels in virus-transformed animal cells, at low levels in the normal cells, and at elevated levels in human tumors.
   3. DNA infectivity assay. Through use of a transfection assay, many active human tumor oncogenes have been identified by their capacity to transform cells to a neoplastic phenotype. These tumor oncogenes are of cellular origin; tumor and viral oncogenes are homologous to normal cellular DNA sequences. Over 100 oncogenes described.
   4. Functions of oncogenes involve signal transduction pathways. They may:
      a. Mimic peptide growth factors - sis (an oncogene) and PDGF (acytokine growth factor).
      b. Imitate occupied growth factor receptor - v-erb-B2 (HER2/neu), a mutated epidermal growth factor receptor, acts as a EGF-R kinase. Importance in prognosis, and treatment of breast cancers by antibody to HER2/neu.
      c. Act directly on signal transduction pathways - ras family.
      d. Activate intranuclear transcription factors
      e. Alter cell cycle regulation.

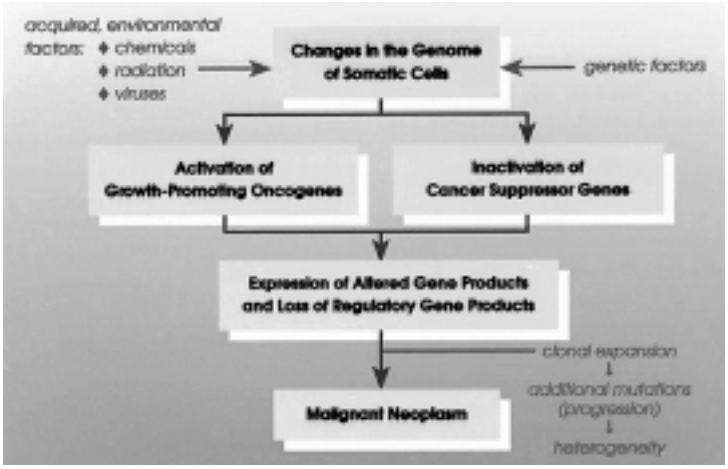
C. Can tumors result from alterations in the structure or control elements of normal growth genes? You bet they can. Relationship to chemical and other forms of carcinogenesis. Two general mechanisms (Figure 3).



   1. Qualitative changes in the oncogene – point mutation in the ras oncogene resulting in decreased GTPase activity; this turns ras on permanently. Many chemical carcinogens act in this manner.
   2. Quantitative increase in oncogene activity.
      a. Gene amplification - N-myc on chromosome 2. Repeated replication of gene gives rise to neuroblastomas, a pediatric cancer arising in the adrenals or in sympathetic ganglia.
      b. Translocation of myc to a "hot" area - 8:14 & other translocations involving myc and 1 of 3 immunoglobulin regulation sites in Burkitt's tumor, a type of lymphoma most often seen in sub-Saharan Africa, so oncogene is permanently activated by one of the Ig enhancer sites; another important example of translocation resulting in oncogenesis is the 9:22 ABL/BCR fusion product in chronic myelogenous leukemia (CML), a fusion protein that is an activated tyrosine kinase. Targeting of the ABL/BCR tyrosine kinase by STI571 (imatinib mesylate).
   3. Therefore, anything that induces a mutation (radiation, chemicals, etc), or DNA

repair, or causes some DNA breakage can activate an oncogene or inactivate a suppressor gene. Relationship of hereditary and environmental factors to oncogenesis. DNA caretaker gene mutations increase the instability of all genes.

4. For instance: interactions of various factors in:
    a. Burkitt's lymphoma: malaria causes B cell proliferation. EBV infection then induces immortalization of B cells. Subsequent translocation moves myc to critical site where it is activated.
    b. Colon carcinoma: transformation of normal colon to precancerous polyp, then to carcinoma involves a series of changes in oncogenes and tumor suppressors (Figure 4). Detection of mutant APC genes in feces as specific diagnostic test for colon cancer



D. Why are there oncogenes? Necessary periods of rapid growth such as morphogenesis, and wound healing. Relationship between oncs and growth factors. Those nasty mutations that cause cancers are probably the price we continually pay for having evolved from the status of slime molds. Maybe it's worth it.

E. The future - microarray technology. Fragments of genes are placed on a matrix as a microarray that is then hybridized with cDNA made from mRNA of cancer cells. Permits estimation of relative expression of genes tested. Can be used to discover genes important in genesis of a cancer, the diagnosis and determining the prognosis of cancers.